REMARKS

Claims 1-11, 13, 14, 18, 19, and 25-62 were preciously cancelled. Claim 21 was previously withdrawn. Applicants reserve the right to file divisional and continuation applications directed towards the cancelled and withdrawn subject matter. Claim 12 has been amended. Support for the amendment can be found throughout the specification, specifically at in the claims as originally filed. Claims 12, 15-17, 20, 22-24, 63, and 64 are currently under consideration.

Rejection Under 35 U.S.C. §112, First Paragraph

Claims 12, 15-17, 20, 22-24 and 63-64 are rejected under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the enablement requirement for the reasons articulated in the previous Office Action. In response to Applicants' previously submitted arguments, the Examiner states that there is no teaching in the specification of the treatment of HCV infection with glycolipids. The Examiner states that Applicants have not demonstrated that glycolipids themselves treat any disease, including HCV. *See* Office Action pages 4-7.

Applicants respectfully traverse the rejection and maintain that claims 12, 15-17, 20, 22-24 and 63-64 are fully enabled by the specification. The enablement requirement of § 112 is satisfied when an application describes a claimed invention in a manner that permits one of ordinary skill to practice it, without undue experimentation. MPEP § 2164.01. Thus, the mere fact that experimentation *might* be required is insufficient to support an enablement rejection. Further, even complex experimentation is not necessarily undue. MPEP § 2164.01.

Applicant respectfully submits that no experimentation is required to make and use the invention of claim 1. Nonetheless, even if experimentation might be required, it would not be undue. In this regard, it is important to be mindful that the question of enablement is one of predictability in view of what is known in the art. Consequently, the amount of guidance or direction needed to satisfy the enablement requirement is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. MPEP § 2164.03.

The specific question of whether experimentation is "undue" is determined based on the following eight Wands factors:

1. Breadth of the claims;
2. Nature of the invention;
3. State of the prior art;
4. Level of ordinary skill in the art;
5. Predictability of the art;
6. Amount of direction provided in the specification;
7. Any working examples; and
8. Quantity of experimentation needed relative to the disclosure.

MPEP § 2164.01(a), citing *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Further, a proper analysis of whether any experimentation is undue requires an analysis of all of the pertinent *Wands* factors. (MPEP § 2164.01(a)). It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. *Id.*

Applicants continue to assert that the claims satisfy the enablement requirement. Claim 12 was previously amended to recite a process for treating a disease in a mammalian subject comprising administering to said subject an effective amount of an intermediary metabolite or a reagent that increases the intracellular or extracellular or serum level of a mammalian intermediary metabolite in said subject, where such increase results in a change in the immune profile of subject. The claim is presently amended to clarify that the intermediary metabolite is a glycolipid. As taught in the specification, such immune parameters may include cellular, humoral or cytokine elements, and the modulation or change can be specific or non-specific. As discussed in detail in previous responses, practicing the present invention is strictly a question of administering a glycolipid to an HCV infected patient and the only experimentation that may be required is the particular dosage to be used. As is well known, dosage questions are considered to be part and parcel of routine experimentation and do not represent undue experimentation. Furthermore, some guidance for appropriate levels is even presented in the specification: ""For example, the metabolite level of a subject can be considered to be a guide for such levels" [0034].

With regard to the *Wands* factor of "Nature of the Invention", Applicants respectfully

assert that amended independent claim 12 is now directed towards a method for treating HCV comprising administering an effective amount of an intermediary metabolite or a reagent that increases the intracellular or extracellular or serum level of a mammalian intermediary metabolite in said subject, wherein said intermediary metabolite is a glycolipid, the increases resulting in a change in the immune profile of subject, and wherein said disease is cancer, a viral infection, or an autoimmune disease.

With regard to the *Wands* factor of "Breadth of the Claims", the Applicants wish to remind the Examiner that Applicants elected the virus of HCV in the response to restriction requirement filed August 2, 2005.

Considering the *Wands* factor of "Presence or absence of Working Examples and Amount of Direction or Guidance Present", Applicants respectfully disagree with the Examiner's statement that "...all Applicants has is a nexus among the immune profiles of normal and Gaucher's patients that are either infected or uninfected with HCV. Applicant has not demonstrated and evidences that glycolipids itself treats any disease, including HCV." *Id.* at page 4. It appears that the Examiner makes this conclusion because "the specification contains neither an in vitro nor an in vivo study demonstrating that glycolipids treat HCV infection..." *Id.* As articulated in the previous response, Applicants respectfully direct the Examiner's attention to the following passages (page 14, line 24 - page 15, line 16 of the originally filed specification; paragraphs 38 - 40 of the published version of the specification (U.S. Patent Application Publication No. 20040171527)):

> [0038] In one embodiment, this invention provides a process for treating a disease in a mammalian subject, e.g. a human, in which an effective amount of a mammalian intermediary metabolite or reagent is administered to the subject. By doing so, the intracellular or extracellular or serum level of the metabolite in the subject is raised. The intermediary metabolite can comprise lipids or conjugated biomolecules. The latter can take the form of glycolipids, lipoproteins and glycoproteins other than antibodies, cytokines or hormones. Such glycolipids can, in turn, comprise a monosaccharide ceramide, e.g. glucosyl ceramide or galactosyl ceramide.

> [0039] Administration of the intermediary metabolite or reagent, as described further below, can be carried out by conventional means known in the art, including intravenous means, intramuscular means, or oral means
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> [0040] In terms of the diseases that can be treated in accordance with the present invention, these include cancers, infections and immune dysfunctions. Infections can be varied and include those whose etiology is viral or bacterial in nature. Viral infections include, for example, HBV, HCV and HIV.

Applicants assert that the above passages indicate that HCV as an appropriate disease candidate for the methods of the current invention. These passages also indicate that glycosylceramides are appropriate reagents to carry out this treatment. The specification states that: (1) HCV is an appropriate disease target: (2) the administered compound is a glycolipid; and (3) treatment consists of administration of the glycolipid. In addition, the specification describes experimental results showing that glycolipids cause a change in the immune profile of subject. *See*, for example, page 9, line 3 - page 13, line 3 and page 17, lines 18-23 of the originally filed specification (paragraphs [0024] - [0032] and [0055] of the published version of the specification (U.S. Patent Application Publication No. 20040171527)).

Applicants have analyzed the data from both normal and Gaucher's patients and have reasonably concluded that the differences in profile (*i.e.*, when there is also an HCV infection present that is favorable in the Gaucher's patients) is due to an overabundance of glucosylceramide (the hallmark and causative agent of Gaucher's disease). On this basis, Applicants have made a reasonable conclusion that mimicking this effect in an HCV infected individual by artificially raising the levels of glucosylceramide also confers benefits that are achieved in a natural state by Gaucher's patients. There is no contradictory evidence available that demonstrates that the conclusion of the Applicants' is improper.

In addition, although the specification contains no working examples, data is included illustrating the immune profiles of normal and Gaucher's patients that are either infected or uninfected with HCV. This data allowed the inventors to conclude that emulation of the Gaucher's condition, *i.e.*, artificially heightened levels of glycolipids, would emulate the beneficial immune responses to HCV which are similar to that of a Gaucher's patient. As such,

the artificial administration of glycosylceramides to HCV patients to achieve such a result is in the nature of a prophetic example. *See* originally filed specification at page 9, line 3 - page 13, line 3 and page 17, lines 18-23 (paragraphs [0024] - [0032] and [0055] of the published version of the specification (U.S. Patent Application Publication No. 20040171527)).

The Examiner states on page 5 of the Office Action that "Applicant's claimed invention is merely an invitation for the skilled artisan to blindly experiment..." Applicants again assert that only the particular delivery route and dosage need to be determined. As previously articulated, the term "treatment" only describes a particular action, *i.e.*, the administration is the treatment. Benefits that would be achieved by application of this treatment would only be related to the utility of such treatment. Applicants have taught as a prophetic example that the result of such a "treatment" will be a beneficial effect with regard to immune responses to HCV. Thus, endowment of any particular degree of benefit by this treatment would have utility. This is much lower bar than a claim for a cure.

Applicants also continue to assert that the specification clearly teaches the administration of glycolipids for the treatment of HCV. The administration of glycolipids is taught in paragraphs [0021], [0035], [0038] and [0046]; means for administration of a glycolipid are described in [0033], [0039] and [0042] and the specific utility of such administration for HCV is described in [0032], [0036], [0040] and [0043] (U.S. Patent Application Publication No. 20040171527)). In short, the specification prophetically teaches that benefits for HCV subjects will be achieved by administration of a glycolipid.

The Examiner again states on page 8 of the Office Action that "...Applicant has not demonstrated nor evidenced that the administration of glycolipids treats HCV." Applicants assert that this statement is only a partially correct in that the specification teaches the administration of glycolipids for treatment of HCV by affecting a change in the immune profile of a subject but does not demonstrate the administration of glycolipids as being effective in treating HCV. It appears that the Examiner is concluding that the enablement requirement would be satisfied only if the specification: (1) contained a physical demonstration that administration of a glycolipid was beneficial in treating HCV; (2) described experiments characterizing the roles of innate and antigen-specific immune responses to HCV; or (3) described a specific

immune parameter that particular metabolite/glycolipid modulates and how the modulation results in the treatment of HCV. Prophetic exemplification is considered appropriate unless there is definitive evidence that the method will not work as described or it there is insufficient teachings of how to accomplish the method. MPEP 2164.02. The desired result of the present claims (treatment of HCV and altering the immune profile of a subject) would be accomplished by the single step of administration of the appropriate dosage of a glycolipid.

In regards to the *Wands* factor of "State of the Prior Art", the Examiner on page 9 of the Office Action comments on the lack of characterization of innate and antigen specific immune responses. Applicants respectfully assert that he claims contain no limitation concerning innate or antigen-specific immune response. Further characterization of these effects is not necessary in practicing the invention nor would the lack of further characterizations hinder carrying out the present invention. This alleged "lack of characterization" does not appear to be relevant to the question of whether a skilled artisan has the ability to practice the present invention. The only advantage of further characterization of these parameters would be for the development of theoretical predictions. An inability to link the effects of glycolipids to innate and antigen specific immune response to HCV does not affect the claimed method of increasing intracellular or extracellular serum levels of an intermediary metabolite resulting in a change in the immune profile. A lack of a complete characterization of these factors will not disallow administration of a glycolipid, *i.e.*, a more clear and complete understanding will not assist a skilled artisan in the administration of a glycolipid to change immune parameters. It is unclear to Applicants what particular challenges of administering glycolipids to an HCV infected subject are raised by the absence of a complete characterization of immune response to HCV. As noted previously, the incomplete characterization of innate and antigen specific immune responses to HCV neither hinders or benefits the practice of the present invention and thus does <u>not</u> "contribute to challenges that the skilled artisan would encounter in attempting to practice the claimed invention..." *Id.*

The Examiner later states "Thus, for a skilled artisan to practice the claimed invention, the skilled artisan would have to demonstrate that glycolipids treats HCV, something that Applicants should have all ready provided in Applicants' disclosure." *Id.* at page 10. Again,

Applicants reiterate that practicing the invention would not require demonstration of effectiveness.

The Examiner comments on the lack of information provided in the specification detailing the modulation of specific immune parameters. *Id.* at pages 12 and 15. As articulated previously, these parameters are discussed as follows (page 17, lines 18-23 of the originally file specification; paragraph 55 of the published version of the specification (U.S. Patent Application Publication No. 20040171527)):

> [0055] Yet another aspect of the present invention is a process for treating a disease in a mammalian subject, e.g., a human, comprising the step of administering to the subject an effective amount of a mammalian metabolite so as to modulate or change at least one component in the immune system of the subject. Such an immune system component can comprise cellular, humoral or cytokine elements, and the modulation or change can be specific or non-specific.

Applicants respectfully assert that description of these parameters is not required to practice the invention, as any active role with the patient is complete after administration of a glycolipid to a subject.

Applicants also assert that the claims do not require the presence of a mechanism describing how administration modulates the immune system. Figures 1 - 6 demonstrate several altered immune parameters in Gaucher's patients which appear to decrease detrimental effects caused by the immune response to HCV infection. It is expected that one or more of these same parameters will be beneficially altered in HCV patients. Again, the Examiner does not consider the word "treat" to indicate the act of administering the intermediary metabolite. Instead, the Examiner is requiring the phrase "treats" in itself to indicate "provides benefits". As discussed above, Applicants' specification teaches that benefits should be achieved by administration of glycolipids to HCV infected individuals after consideration of the differences in immune profiles in normal and Gaucher's patients.

The Examiner again notes the lack of an *in vitro* nor an *in vivo* study demonstrating that glycolipids treat HCV infection. *Id.* at page 16. A specific demonstration that glycolipids treat HCV infection is not required to practice the invention. The Examiner further states that the skilled artisan would not be able to demonstrate that glycolipids treat HCV without undue

experimentation. *Id.* These statements concern issues in evaluating the results of the treatment **after** carrying out the present invention, rather than the ability of a skilled artisan to use the invention. Events which occur after practicing a claimed method are not an element of a proper *Wands* analysis.

The Examiner states on page 17 "In order for the skilled artisan to successfully practice the claimed invention, the skilled artisan would have to blindly and unduly experiment with glycolipids, each immune component, and determine the relationship among glycolipids, each immune component and HCV infection." Applicants disagree and assert that each immune component is not a factor that may be manipulated independently from administration of the glycolipid. As discussed previously, administration of the glycolipid in itself causes effects on the immune components of the subject and as such these are intrinsic effects induced by the administration of the glycolipid. Measurements of immune components (rather than independent manipulations thereof) are only useful for assessments of the effectiveness of various doses of glycolipids in a subject.

Applicants have repeatedly asserted that "demonstration" is not required to show that the present invention is enabled. Post-filing publications describe experimental data produced from the administration of glycolipids with regard to the disease manifestations induced by HCV infection. *See*, for example, Safadi *et al.*, 2007, Int. Immunol. 19; 1021-1029 (describing amelioration of hepatic fibrosis by glucosylceramide); Zhang *et al.*, 2009, Clin. Immunol. 157; 359-364 (describing successful treatment of autoimmune cholanitis, similar to human biliary cirrhosis); and Zigmond *et al.*, 2009, Am. J. Physiol. Endocrinol. Metabo. 296; E72-E78 (describing improvements in hepatic steatosis after administration of β-glucosylceramide, or betalactosylceramide). These publications demonstrate that administration of glycolipids do provide relief for pathogenic inflammatory processes that are also present during HCV infections.

In view of the foregoing, Applicant respectfully submits that ordinarily skilled artisans would be able to make and use the claimed invention, despite any experimentation that might be required. The specification contains examples of a change in the immune profile of a subject due to the presence of increased levels of glycolipids (page 14, line 24 - page 15, line 16 of the

originally file specification; paragraphs 38 - 40 of the published version of the specification (U.S. Patent Application Publication No. 20040171527)). In addition, methods for evaluating the effectiveness of an HCV treatment are well known to one of skill in the art. Such methods are routinely utilized in clinical trials with humans and chimpanzees and would require no undue experimentation. Parameters used to judge efficacy (*i.e.*, evaluating success) are well known in the art given the amount of research available in evaluating potential approaches to treat HCV. In addition, dosage questions are considered to be part and parcel of routine experimentation and do not represent undue experimentation. Furthermore, some guidance for appropriate levels is presented in the specification. Thus, the conclusion that the specification is fully enabling is buttressed by the amount of knowledge in the state of the art and the majority of *Wands* factors that weigh in favor of enablement. Therefore, the present application adequately enables the claimed invention.

Applicant thus respectfully requests favorable reconsideration and withdrawal of the rejection under 35 U.S.C. § 112.

Conclusion

It is believed that claims 12, 15-17, 20, 22-24, 63, and 64 are now in allowable form. Accordingly, a timely Notice of Allowance to this effect is earnestly solicited.

The Examiner is invited to contact the undersigned at 412-918-1116 to discuss any matter concerning this application.

The Office is hereby authorized to charge any additional fees or credit any overpayments under 37 C.F.R. § 1.16 or § 1.17 to the previously authorized deposit account number 50-0525.

Respectfully submitted,

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